

WE CLAIM:

1. An isolated protein complex including a combination of at least two proteins selected from the group consisting of GRF2, GRF2-Interacting Proteins, Ndr-Interacting Proteins, Skb1-Interacting Proteins, PP2C-Interacting Proteins, pICln-Interacting Proteins, 4.1SVWL2-Interacting Proteins, smD1-Interacting Proteins, and smD3-Interacting Proteins.
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2. The isolated protein complex according to claim 1, wherein the proteins are each of mammalian origin.
3. The isolated protein complex according to claim 1, wherein at least one of the proteins is a fusion protein.
- 10 4. An isolated or recombinant protein having an amino acid sequence of a protein represented in Table 1, 2, 3, 4, 5, 6, 7, or 8 or a homolog thereof.
5. An isolated nucleic acid sequence comprising either a full-length or partial coding sequence for a protein of claim 4.
- 15 6. A method for identifying modulators of protein complexes, comprising the steps of:
 - (i) forming a reaction mixture including a protein complex of at least two proteins selected from the group consisting of GRF2, GRF2-Interacting Proteins, Ndr-Interacting Proteins, Skb1-Interacting Proteins, PP2C-Interacting Proteins, pICln-Interacting Proteins, 4.1SVWL2-Interacting Proteins, smD1-Interacting Proteins, and smD3-Interacting Proteins,
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 - (ii) contacting the reaction mixture with a test agent, and
 - (iii) determining the effect of the test agent for one or more activities selected from the group consisting of:
 - (a) a change in the abundance of the protein complex;
 - (b) a change in the activity of the complex;
 - 25 (c) a change in the activity of at least one member of the complex;
 - (d) where the reaction mixture is a whole cell, a change in the intracellular localization of the complex or a component thereof;
 - (e) where the reaction mixture is a whole cell, a change in the transcription level of a gene dependent on the complex;

5 (f) where the reaction mixture is a whole cell, a change in the abundance of the product of a gene dependent on the complex;

(g) where the reaction mixture is a whole cell, a change in the activity of the product of a gene dependent on the complex; and,

(h) where the reaction mixture is a whole cell, a change in second messenger levels in the cell.

7. A method for identifying an agent which may modulate GRF2 dependent growth comprising:

10 (i) forming a reaction mixture including a protein selected from the group consisting of GRF2-Interacting Proteins, Ndr-Interacting Proteins, Skb1-Interacting Proteins, PP2C-Interacting Proteins, pICln-Interacting Proteins, 4.1SVWL2-Interacting Proteins, smD1-Interacting Proteins, and smD3-Interacting proteins,

15 (ii) contacting the reaction mixture with a test agent, and

(iii) detecting the effect of the test agent for one or more activities selected from the group consisting of:

20 (a) a change in the abundance of the protein complex;

(b) a change in the activity of the complex;

(c) a change in the activity of at least one member of the complex;

(d) where the reaction mixture is a whole cell, a change in the intracellular localization of the complex or a component thereof;

25 (e) where the reaction mixture is a whole cell, a change in the transcription level of a gene dependent on the complex;

(f) where the reaction mixture is a whole cell, a change in the abundance of the product of a gene dependent on the complex;

(g) where the reaction mixture is a whole cell, a change in the activity of the product of a gene dependent on the complex; and,

30 (h) where the reaction mixture is a whole cell, a change in second messenger levels in the cell.

8. The method according to claim 6 or 7, including the further step of formulating one or more of the agents identified in the assay with a pharmaceutically acceptable excipient.

9. A method for altering the growth state of a cell comprising contacting the cell with an agent identified according to the assay of claim 6 or 7.

10. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an agent identified according to the assay of claim 6 or 7.

5 11. A method for inducing differentiation of a cell comprising contacting the cell with an agent identified according to the assay of claim 6 or 7.

12. A method for reducing the severity of a condition involving Ras-dependent proliferation of cells, comprising administering to an animal having said condition a therapeutically effective amount of an agent identified according to the assay of claim 6 or 7.

10 13. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an agent capable of inhibiting the activity of a member of the Ras signaling pathway.

14. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an inhibitor of a methyl transferase activity of Skb1.

15 15. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an inhibitor of a kinase activity of Skb1.

15bis. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an agent that inhibits normal subcellular localization of Skb1.

20 16. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an inhibitor of a phosphatase activity of PP2C.

17. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an inhibitor of an activity of pICln.

18. A cellular host that is engineered genetically to produce a protein according to claim 4.

19. A method for detecting aberrant GRF2-dependent signaling in a cell, comprising the step 25 of screening the cell for one or more of:

(i) altered levels of expression of a gene encoding a GRF2-Interacting Protein, an Ndr-Interacting Protein, an Skb1-Interacting Protein, a PP2C-Interacting Protein, a pICln-Interacting Protein, a 4.1SVWL2-Interacting Protein, an smD1-Interacting Protein, or an smD3-Interacting protein,

30 (ii) altered levels of stability, post-translation modification, cellular localization and/or enzymatic activity of a GRF2-Interacting Protein, an Ndr-Interacting Protein, an

Skb1-Interacting Protein, a PP2C-Interacting Protein, a pICln-Interacting Protein, a 4.1SVWL2-Interacting Protein, an smD1-Interacting Protein, or an smD3-Interacting protein, and

5 (iii) altered levels of activity of a complex including a GRF2-Interacting Protein, an Ndr-Interacting Protein, an Skb1-Interacting Protein, a PP2C-Interacting Protein, a pICln-Interacting Protein, a 4.1SVWL2-Interacting Protein, an smD1-Interacting Protein, or an smD3-Interacting protein.

20. 20. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an inhibitor of a kinase activity of Ndr.

10 21. A method for inhibiting Ras-dependent proliferation of a cell comprising contacting the cell with an agent that inhibits normal subcellular localization of Ndr.

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